Large Scale Bio- Manufacturing

How to comply with GMP and Biosafety regulations:

In one place,
At the same time,
With one product,
with the same people,
. . . . . . ?

Per Staugaard, December 2016
Biosafety

• Definition
A combination of procedures, containment systems and construction technologies with the purpose of minimizing the risk of infecting laboratories and prevent escape of microbes into the surrounding environment

• Purpose
- To create a safe environment in which to research infectious diseases
- To prevent escape of infectious agents
- To minimize staff member’s and other people’s contact with infectious agents both within and outside the containment zone
- To prevent the introduction of infectious agents into the nature
The full spectrum of the global challenge: biosafety

Biological risks can be seen as a spectrum:

- Naturally Occurring Pandemic
- Reemerging Infectious Diseases
- Unintended Consequences of Research
- Laboratory Accidents
- Lack of Awareness
- Policy Choices
- Negligence (Failure to Follow SoPs)
- Crime & Counterfeit Drugs
- Sabotage
- Attack Leading to Release
- Biowarfare Terrorism State BW

Natural  Accidental  Intentional

Infection prevention  

Biosafety  Biosecurity

By courtesy of Tim Trevan
Biosafety Guidelines

• Some guidelines take a performance approach
  ➢ Define the intended result (e.g. WHO)

• Other guidelines are more prescriptive
  ➢ Outline specific requirements
  ➢ Acceptance criteria (e.g. Canada and BMBL (USA))
Systems come together

GMP guidelines

EHS regulations

Me

You?

GAPIII system

GAPIII containment

GAPIII biosecurity

Internal and external transport

ISO standards

IATA guidelines
Biosafety - Risk Assessment

- Evaluate
  - Volume
  - Concentration
  - Possible ways of escape
  - Route of transmission
  - Infectious dose
  - Susceptible hosts
  - Incubation period
  - Decontamination principles

Along with all other aspects of product safety
Large Scale Production Risk Assessment

- Due to GMP – we already have...
  - **Closed systems** – a process requirement
  - **Double filters & steam traps** on tanks etc. to keep all contaminating elements out
    - Thereby keeping the infectious agents **within** the tanks
  - **Sterile tube welders** for inoculation and sampling
  - Adequate monitoring and **alarms**
  - **Automatic shut down** in response to critical alarms
  - **cGMP procedures**
    - Batch records, GMP trained employees, SOPs, log books, etc.
Biosafety $\leftrightarrow$ GMP

**GMP**

- BSL1
  - Basic hygiene & Common sense

- BSL2
  - + standard precautions
    - primary process & primary containment

- BSL3
  - + specific measures
    - based on RA – including secondary process

- BSL4
  - + ... redundancy

**BioSafety**

Need for specific solutions

Need for specific and creative solutions
Bio-Occupational Health strategy

- Source
- Technical measures
- Organization
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis
Bio-Occupational Health strategy

- Change material: safer strain
- Technical measures
- Organization
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis
Bio-Occupational Health strategy

• Change material: safer strain
• Containment [Primary & Secondary]
• Organization
• Hygiene
• PPE
• Vaccination
• Post exposition prophylaxis
Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis
Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hand wash: prevent spreading in environment [shower out]
- PPE
- Vaccination
- Post exposition prophylaxis
Bio-Occupational Health strategy

• Change material: safer strain
• Containment
• Training, SOPs, access control
• Hand wash: prevent spreading in environment [shower out]
• Coat/gown, gloves, glasses, respirator, . . .
• Vaccination
• Post exposition prophylaxis
Bio-Occupational Health strategy

• Change material: safer strain
• Containment
• Training, SOPs, access control
• Hand wash: prevent spreading in environment [shower out ]
• Coat/gown, gloves, glasses, respirator, . . .
• Vaccination: necessary & sufficient
• PEP: very much dependant on organism
Bio-Occupational Health strategy

- Change material: safer strain
- **Containment**
- Training, SOPs, access control
- Hand wash: prevent spreading in environment [shower out]
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Self contained equipment
containment & procedures

- fermenter/culture bottle/egg
- down stream processing
- biosafety cabinet
- primary containment
- Restricted entrance
- training/qualification
- Information
- Personal protection
- secondary containment
- HEPA filter
- medical control & vaccination; post exposition treatment
Biosafety – GMP: Synergies

• Restricted access
• Segregation of production areas
• Facility designed for easy cleaning
• Minimize contaminants
• Validate processes, systems, equipment, and facilities
• Job certification and mandatory training
• Mandatory personal protective equipment (PPE)
• Written policies and procedures
• Documentation, double signatures, etc.
cleanroom

fermenter/culture bottle/[egg]
downstream processing
LAF unit

Closed system
Restricted entrance
training/qualification
Information

Gowning Procedures

Classified Cleanroom

medical control & vaccination to protect products
GMP and Biosafety Clashes
Then what?

• Read the guidelines
  ➢ Understand them
    • Not only **what** they say –
    • But also **WHY** they say it

• Is there another way to do it?
• Risk assessments
• Decide on a solution
• Brace yourself to face the authorities
HVAC

Room & Building layout

Waste

Pressure differences
HEPA filters

Process

Cold Work / Storage

Warm Incubation

Training & qualification

Personal protection

Personnel

Choice of Equipment

Equipment special design

Liquids
EDS [Killtanksystem]

Solids
autoclaving; incineration
Pressure difference
unidirectional airflow

Positive Pressure
Negative Pressure
Pressure difference
unidirectional airflow

Positive Pressure

Negative Pressure

“standard cleanroom”
Pressure difference
unidirectional airflow

“standard BSL-3 lab”

Positive Pressure
Negative Pressure
Positive Pressure

Negative Pressure

dedicated design with “safe biopositive room”
Pressure difference
unidirectional airflow

Positive Pressure
Negative Pressure

BSL – solution with overpressure protection in airlock
Pressure difference
unidirectional airflow

Positive Pressure

Negative Pressure

Clean shell around bio + rooms
Pressure difference
unidirectional airflow

Positive Pressure
Negative Pressure

Biosafety shell around clean room